MAX FINK

Interviewed by David Healy

Phoenix, Arizona, December 8, 2008

DH: Today is the 8th of December, 2008. This is the ACNP Annual General Meeting in Phoenix, Arizona and I'm David Healy, here to interview Max Fink.

MF: Good morning.

DH: Can we begin with where you were born and how you ultimately went into medicine?

MF: I was born in Vienna on January 16, 1923. My father was a medical student who had just finished his training. My mother was also a medical student whose training was interrupted by her pregnancy with me. Soon after I was born, my father came to America for an internship. My mother and I lived in Vienna and a year later we immigrated to New York. My schooling was in an elementary school, PS 77, in the Bronx and then, high school, James Monroe HS, nearby; both within walking distance from our apartment just above my father's office. He was a general practitioner serving a community of working families, caring for them from birth to death. He had special training in radiology in Vienna and had an x-ray in one room of his office. He also had an early electrocardiograph and a busy clinical laboratory. As a teen-ager, I was often called to develop films, help in setting fractures, and do simple laboratory tests of urine and blood. I always assumed that I would follow him in medicine, even knowing that admission to medical school was very difficult as a Jew. I finished elementary and high school early, graduating at 16 in January, 1939. I enrolled in New York University at their University Heights campus, graduating in June 1942, after three years of college. I was admitted to New York University's School of Medicine on December 6, 1941, the day before Pearl Harbor. With the war the government took over and I became a soldier, Private First Class; so my medical school training was under military auspices. When I graduated on June 12, 1945 I received both my MD degree and my appointment as First Lieutenant in the Army Medical Corps.

My medical school training was a very interesting experience because few trained physicians were available to teach. At Bellevue Hospital I was taught by women and

older physicians who were not called to military duty. Bellevue Hospital had its own army hospital in Europe and all our leading professors were over there. As a consequence, I learned to be an "interventionist". I like that word, because I dealt with maggots and osteomyelitis, blood samples, spinal taps, including cervical 4th ventricular taps in people with neurosyphilis.

My internship at New York City's Morrisania Hospital was equally interesting because I participated in an experiment. I worked on a pulmonary medicine ward that had about twenty patients with empyema. To treat empyema in those days one took a trocar, pushed it into the chest, pulled out the pus, put in saline two or three times until clear fluid came back. This was done every day or every other, day. The clinician in charge, Dr. Eli Rubin, was carrying out an experiment, injecting either a known sulphonamide antibiotic or an unknown new agent "Compound X". The unknown agent was so precious that it was kept in a safe in the director's office. I was responsible for assigning each new patient to one treatment or the other; the even numbered patients would get one treatment, the odd numbered, the other. Within two weeks, it was obvious that patients who received the new drug were doing considerably better; the fluid was thinner, the appetite was better, the fever less. It was one of the first experiments with penicillin. We had an interesting time when a young Puerto Rican woman came in with her baby. When her assignment was to sulphonamide, contrary to law and rules, I switched her to compound X. Maybe a week later, the physician in charge, sees the numbers and says, "This is remarkable; hmm, she's doing very, very well. She shouldn't be, right? What did you do? How did you treat her?" And, he took a look at the number and he took a look at what I had done and he said, "You broke the code." I was in tears. I was taken down to the director's office and the director said, "Well, you're suspended; you didn't obey orders". I didn't know what to do. I called my father and told him the story. He called the Director and negotiated a better resolution; I believe I lost my salary for the month, probably $25.00.

My residencies were also interventionist. The first was at Montefiore Hospital and as a new neurology resident I was the youngest and the most junior member on the service. The neurosurgeon was Leo Davidoff, who had been superbly trained; he had an international reputation and patients came to see him from all of the Americas. He

practiced percutaneous carotid angiography and the neurosurgery residents taught me how to find the carotid artery, introduce the needle, take out the stylet, put in the syringe, inject the radioopaque dye and obtain three immediate x-ray pictures. It was a great experience. My next residency was at Bellevue in neurology. On neurology rounds I see a patient for whom an angiogram would be useful, and request it. The director says that it is not available. I explain that it is simple to do and Professor E. D. Friedman suggests I work out the details with the radiologists. With a fellow resident, Joseph Stein, we negotiate the x-ray agreement and build a box to hold the three x-ray plates. Our first patient had a subdural hematoma and the anterior-posterior view on the angiogram showed the blood vessels nicely pushed aside. From then on Joe Stein and I did a hundred and five angiograms and published two papers on carotid angiography. This interventionist experience was a strong basis for my interest later in EEG.

DH: How did you move from there to the mental health field?

MF: While I was at Bellevue, I had two well-known teachers. One was Bernard Dattner, a student of Wagner-Jauregg, the 1927 Nobel Prize winner in Medicine for work on fever therapy in neurosyphilis. Dattner was a Jew who had left Vienna for America because of the Holocaust to join the NYU faculty. I was a student with him in 1944. He ran the neurosyphilis clinic and taught me how to do fourth ventricular taps. That was an intervention where patients lie on their left side, bend their neck forward with chin on their chest, and the doctor puts a needle between the vertebrae to withdraw spinal fluid from the 4th ventricle. It took me awhile to realize that if I went another inch, I would be pithing a human, but Dattner said, “Don’t worry, you’ve got plenty of space”. So I collected CSF for a couple of months. He also taught me a lot about fever therapy and the colloidal gold test for neurosyphilis. We treated patients in fever boxes, sweating them for hours; my job was to monitor fluid intake and body temperature.

At the same time, I was taught also by Morris Bender. He became the chairman of neurology at Mt. Sinai Hospital and was, for many years, president of leading organizations in neurology. Bender was interested in sensory stimulation and physiology. While in the Navy, he had a patient with a lesion in the parietal lobe. As he was doing sensory tests he found that, when two stimuli were applied in the visual or the somatosensory field, the patient would appreciate only one stimulus; the other was

“extinguished”. Extinction was demonstrated in visual field tests on patients with occipital lobe lesions. Bender put me and other residents, Martin A. Green and Joseph Jaffe, to work in double simultaneous cutaneous sensory stimulation tests. My first research papers, a whole series, described the Face Hand Test, Double Simultaneous Stimulation in Patients (DSS) with Mental Deficiency and the use of the tests in children. The most interesting study was development of a test for the "organic mental syndrome." Patients with diffuse brain disease made errors of extinction and displacement on simultaneous stimulation. If the patient seemed to have a brain lesion and the simple DSS test was ambiguous, we gave intravenous amobarbital, and the double simultaneous extinction phenomena became obvious. We published this clinical test which is still recommended for detection of a “soft” neurological sign. At one point, we thought of applying the test to patients getting insulin coma or electroshock.

Bender suggested I obtain an appointment at Hillside Hospital, a sister Federation institution on Long Island, dedicated to psychiatry that had a new residency program. I hadn’t intended to take another year of residency but I visited the hospital and I was very pleased with what they offered me, which was residency for a year, focused on psychodynamic psychotherapy. It began in January 1952. I had already become interested in psychoanalysis by attending classes at the William Alanson White Institute during my neurology residencies.

I joined Hillside Hospital on January 2, 1952, and my first assignment was to the ECT service. ECT was given three days a week and, at the same time, the resident supervised the adjoining insulin coma therapy (ICT) unit. Never having seen ICT and never having given ECT I was the student assigned to do it. The Attending Psychiatrist, Simon Kwalwasser, taught me how to administer ECT and walked me through ICT for two or three days and then said, “You’re in charge of both ECT and ICT”. I was perfectly happy to be in charge of 22 beds for patients in insulin coma every morning, five days a week, and giving eight to ten patients ECT. The patients received insulin injections from nurses at 6:00 am. When I came in at 7:30 or 8:00 am the patients were already stuporous. At about 9:00 or 10:00 in the morning we tested whether they were in coma and wrote the time on a chalkboard at the foot of the bed. Sixty minutes later, the nurses called me to administer glucose either by gavage or intravenously. It was a

remarkable experience to see a patient in deep stage IV coma, without pupillary or deep tendon reflexes and unresponsive to pain, speak within 15 minutes and become fully oriented. I spent the afternoons doing psychotherapy under the supervision of accredited New York psychoanalytic psychiatrists.

While in the Army I was assigned to a field aid station in a company of the 2nd Infantry Regiment. One day I was called to headquarters and given orders to attend the Army's School of Military Neuropsychiatry at Fort Sam Houston. To this day, I have no idea why I was selected. I attended the school for four months; one-third the course was training in psychoanalysis, one-third in general psychiatry, and one-third neurology. One of the teachers was Gilbert Glaser, the Neurology Chairman at Yale for many years. We learned a great deal. In my group were three or four doctors interested in psychoanalysis. I look back and wonder how did that come about, but the reality was that everyone at that time thought psychoanalysis was the future of psychiatry. Indeed, when I was in neurological training at Bellevue, I decided to attend an analytic school at the same time. I was aware of the philosophical barrier among neurologists for psychoanalysis. If I had gone to Morris Bender, E. D. Friedman or Bernhard Dattner and said, "I'm going to go to psychoanalytic school", I believe I would have been asked, nicely, to take another residency elsewhere. At the time, there was much rivalry and antipathy between the fields. I had visited different analytic schools in New York and one, the William Alanson White Institute, accommodated residents in training with courses given in the evenings and Saturday mornings. One course was in Washington, DC. I would travel by train on Friday night, stay overnight, take a course for a whole day on Saturday with Dr. David McKenzie Rioch and then I would return. I also became acquainted with his wife, Janet Rioch. It was a very intensive course and I graduated in 1953 with a Certificate of Psychoanalysis for Physicians. I also went through four and a half years of personal analysis. In retrospect, it was neither helpful nor harmful; it was quite benign. My analyst, Joseph S. Miller, was very reassuring. My recollection is that I would go three or four times a week, all paid for by the United States government under the G.I. bill. The most fascinating part was that, when I opened my office in 1953 for neurology and psychiatry, I did psychotherapy for a while. I found it boring to sit and listen to somebody talk for forty minutes during the day when, later that evening, I would go into

the next room and induce a seizure in an ECT treatment. After three weeks, the ECT treated patients were better and the psychotherapy patients kept coming back and back but I didn't know how to get them better. This was in the days before we had imipramine or chlorpromazine.

DH: Before we leave the issue of insulin coma, can you walk me through that?

MF: That's another fascinating experience. Insulin coma was a creation of Manfred Sakel, who was Viennese. He had first learned about insulin as a new treatment for diabetes. Insulin was discovered in 1922. In 1928, Sakel was in a hospital in Berlin where he was treating patients with drug addiction, many in opiate withdrawal. They lost weight, vomited, sweated a lot. He decided to give them insulin in order to improve their appetite. After insulin injections the patients calmed down. Next, he went to the University of Vienna where he continued his experiments with insulin and found that these patients would also calm down after insulin. In retrospect, it was probably the patients who were catatonic and depressed that seemed to improve. The definition of schizophrenia in those days was not very specific; it was quite broad and included catatonia as a type of schizophrenia. Every psychotic patient was considered schizophrenic. Insulin coma came to the United States in the late 1930s and Hillside Hospital, where I took my residency, offered the treatment early on.

DH: What year was insulin coma introduced at Hillside?

MF: I think the first time we have records was in 1937 for insulin coma, Metrazol (pentylenetetrazol seizures the same year, and ECT probably by 1940. I am not sure. When I took over the unit in 1952 we offered patients up to fifty insulin comas; the procedure had been well developed and there was a worldwide interest in it. Some doctors offered forty comas; some thirty and some did sub-coma insulin. Every variety of treatment and dosing was tested and reported. My study of ICT was in 1956. I had already introduced chlorpromazine (Thorazine) to Hillside. It was obviously effective in the same patients that we referred to ICT, so I considered a random assignment study. Because it was a psychodynamic hospital, the residents and the attending physicians paid little attention to ECT or ICT. When they sent the patient for ICT or ECT that ended their interest. My unit was a dumping ground where they sent all the older, severely depressed, severely psychotic, and manic patients. We did this random assignment study

in 52 patients, 26 with ICT and 26 with chlorpromazine. Chlorpromazine and ICT were equally effective or equally ineffective because there was about a fifty percent response rate. We didn't go by remission in those days, we went by dischargeability; was the patient well enough to leave the hospital? The results for the two treatments were the same but chlorpromazine was less expensive, did not require four or five hours of nursing care every day, and the risks were much less. My unit had eight or nine nurses for twenty-two patients; it was very labor intensive. When I presented this material to the Attending physicians, they were favorably impressed. I offered to close the insulin coma unit and they agreed. We published the paper in *JAMA* in 1958, and it was well received; I still think it's one of the better papers I've done. It was a random assignment study but we were not blinded. That's the main its limitation, but we did measure the results by the discharge rate, the rating scales and the fact that by the time the study was over, every nurse in the hospital was sending me patients for chlorpromazine. When I arrived on my morning rounds the nurses would walk up to me and say, "Dr. Fink, please see Mr. so and so in my ward". The residents weren't interested initially but eventually began to refer patients for chlorpromazine; that ended insulin coma at Hillside and eventually at other hospitals. Many years later, there was a very famous economist, John Nash who stimulated interest in insulin coma again.

DH: He was famous for game theory.

MF: Right. John Nash of Princeton eventually received the Nobel Prize in 1994 but soon after he published the research that led to the award he became severely psychotic. He had gone to Boston as a Lecturer and was admitted to McLean Hospital where they kept him in psychotherapy for a couple of weeks. As he tells the story, he figured out what they wanted from him, hid his symptoms and they let him go home. He returned to Princeton but relapsed and was admitted to the local state hospital. The best unit in 1961 at a State hospital was the insulin coma unit, with the most nursing care, best food, best qualified doctors. He was treated and recovered dramatically but it didn't carry over because he refused to take the prescribed chlorpromazine and eventually relapsed. The story was told in a fine biography on which a film was based and produced about seven or eight years ago.

DH: It was called *A Beautiful Mind*.

MF: *A Beautiful Mind*, thank you. I received a phone call one afternoon from the author of the book, Sylvia Nasar, "Are you the man who did insulin coma at one time?" she asked. "I've been given your name by the National Institute of Mental Health. I've written this book and we are going to make a film from it, would you be willing to be a consultant"? I had read the book, so, I was pleased to agree. If you look at the credits, I'm the last one, well, not quite; there are two after me. So, I had to tell my friends, please stay to the end!

DH: Did you meet any of the big names in the insulin field, like Manfred Sakel?

MF: I met him, I think, twice. He had been at meetings in the United States, but I did not have any personal relationship with him. I did, however, have a very close relationship with his cousin. When I was an intern at Morrisania City Hospital one of the neurology attendings, a very young man, was William Karliner. When I was at Hillside in 1952, Karliner was also a member of the attending staff and he stopped by the ECT unit a number of times. Together we examined different electrode placements. He would fiddle with the placements long before it became fashionable. It was already known in 1952 that unilateral ECT was different; you could produce a unilateral seizure if you were very careful with the current. Over the next few decades I got to know him well and I'm still in touch with his wife. He died a few years ago. Karliner was Sakel's cousin and described him as rather egotistical, not at all collaborative. Sakel made a lot of money as a physician, which was unusual in those times. He had insulin coma patients who were wealthy and he set up a foundation. Karliner gave me a different image of the man. In the electroshock world I came to know many of the people who were the leaders.

DH: Can we begin to pick up the psychotropic theme? You were involved in some key early trials for chlorpromazine. How did you get to hear about chlorpromazine?

MF: Two years before chlorpromazine, in 1952 at Hillside, I heard about LSD and there were suggestions that an LSD experience was an "open road to the unconscious". LSD offered subjects images and strange thoughts that many believed were expressions from their unconscious. I obtained LSD from Sandoz and recorded the EEG of patients taking LSD. I offered LSD to any psychiatry resident provided they took it in the EEG laboratory under supervision of my team; they would write notes during the experience

and share them with their attending. It was very popular; almost every resident volunteered!

One day, the director of the hospital, Joseph S.A. Miller, handed me an announcement of a symposium on chlorpromazine at Creedmoor Hospital, a State hospital nearby. It was an all day affair, organized by Henry Brill, who was Commissioner of Mental Health for the State of New York. They had received chlorpromazine six months earlier, and had put it experimentally in state hospital. That day I heard Nathan Kline, Herman Denber, Tony Sainz, Sidney Malitz and Sidney Merlis, each a leading figure in psychopharmacology in the late 1950's, presenting their experience. It was a fascinating day with every speaker telling stories of how patients calmed down and were more manageable. At the end of the day, I went to the back of the conference room, met the representatives of Smith, Kline and French, signed a card and requested samples. They sent me one or two hundred tablets and the next day I gave it to patients with psychosis. Within two weeks a nurse asked me to see a patient who was grossly psychotic and to give the patient the drug. We didn't advertise "chlorpromazine", instead we had a code number. I agreed but asked the resident to approve, who replied, "Thank God, yes; I'm not capable of psychotherapy with this patient".

Almost every patient I wanted to treat at Hillside for the ten years I was there was available to me for study. About the nurse and her referral, my father said, "You've got something special there; don't stop; whatever you do, that's a very special something". "Why?" I asked. "Well, nurses are the only ones who observe patients closely", he replied. So chlorpromazine was introduced through this one-day symposium and the willingness of Smith, Kline and French to supply the drug.

A few years later, Donald Klein joined me at Hillside Hospital. We set up an RCT study. We had already studied imipramine by EEG and clinically and had some ideas that imipramine and chlorpromazine were different classes of drugs. We were particularly interested in the fact that the two drugs had different EEG patterns and different effects on behavior and neuropsychological tests. Don, I and the psychologists, Robert L. Kahn and Max Pollack had a team meeting and decided the only way to do an EEG and behavior study properly, was by random assignment. We devised a very simple study; every patient referred to us for medication was randomly assigned to treatment

with chlorpromazine, imipramine or placebo. The residents could refer patients "for medicine" but could not refer them for a specific drug and they were happy. I keep emphasizing the uniqueness of the environment where almost anything we wanted to do was welcome. The study was designed with EEG monitoring and rating scales. At that time we had the Lorr behavior rating scale and, I think, the Brief Psychiatric Rating Scale (BPRS) of Overall and Gorham. This was before the Hamilton Depression Rating Scale. Over a two-year period, we studied a 144 patients; one third received chlorpromazine, one third imipramine and one third placebo. For six weeks every patient received liquid dosing three times a day: 10, 10, and 20 cc. The concentrations were made up so that impramine dosages were 75, 150, 225, or 300 mg a day; Thorazine doses were 300, 600, 900, and 1200 mg a day and placebo was vehicle only. Both, Geigy and Smith, Kline and French were delighted to give us the chemicals, and it was Smith, Kline and French who gave us the vehicle in which the chemicals were dissolved. For chlorpromazine we added Kemadrin (procyclidine) as an anti-Parkinson agent to mask the extrapyramidal effect of chlorpromazine. The masking was quite good; Don Klein asked every resident to guess which drug their patient received. A small number of patients who had placebo got better and the doctors assumed it was either chlorpromazine or imipramine. Many patients on chlorpromazine thought to be on imipramine and many patients on imipramine thought to be on chlorpromazine. We published our findings in a series of papers over the next few years. Don Klein went on to replicate the study, with the same findings, which is remarkable. I left Hillside in 1962 and Klein went to Columbia University and the New York State Psychiatric Institute where he continued psychopharmacology research.

DH: What were the results of the individual drugs?

MF: Chlorpromazine was a very effective sedating agent for patients with psychosis. It also was a very effective antidepressant for patients who were severely depressed; probably the psychotic depressed. Imipramine had a very good effect on depressed patients. It also had, in young adults, an exciting effect, so we had I think, three or four patients who went into manic states. The placebo had some benefit to some patients, as one would expect, but it was significantly less effective than either of the two drugs. So, we published papers on chlorpromazine as an antipsychotic, imipramine as an

antidepressant and chlorpromazine as an antidepressant. The paper, on the antidepressant effect of an antipsychotic was published in 1962. It was the second paperon te antdepressnat effect of an antipsychotic. The other paper was by Leo Hollister with a different antipsychotic as an antidepressant. I'm not sure which one. That issue of an antipsychotic as an antidepressant has plagued the field for many years and was explained after 1975 when Alexander, Sandy Glassman showed that psychotic depressed people don't respond to imipramine, but do well with an antipsychotic and antidepressant in combination, or, even better, with ECT. In his report, 13 patients who had not responded to imipramine and failed whatever else he were referred to ECT and 12 of 13 remitted. That was the fundamental paper showing that psychotic depression is a distinct entity in the depression spectrum. Since then psychotic depression has been a primary indication for ECT.

DH: It's also worth mentioning, this was the trial that gave rise to Don Klein's idea that there's a condition called panic disorder.

MF: Yes. As I remember it was group of young women who wore raincoats. They were severely phobic, and imipramine did resolve the phobia in some of them. That was another paper that was written from our research. Klein went on to study the issue of panic disorder by a different route. I don't think it was from our studies.

In 1969, I had two outstanding residents at New York Medical College. One, Richard Abrams went on to write about ECT, while the second, Michael Taylor, worked closely with me on catatonia and melancholia. Abrams and Taylor wrote the first important papers on catatonia outside of schizophrenia. They reported catatonia in mania in 1976.

Back to Klein and panic disorder. In 1969, I read a report by Pitts and McClure at Washington University on Lactate Infusion stimulating anxiety disorders. Michael Taylor was my resident at the time and I handed him the paper and I said, "Let's find out if this is true". We went to St. Louis and met Pitts and McClure, saw what they did, and wrote a protocol. We asked Pitts to ship us fluid for lactate imnfusio that he had used and we did an exact replication. We took panic disorder patients and their spouses or siblings, gave both lactate infusions, and confirmed their study very nicely. It was one of those situations, "Do you publish a confirmation, and if so how"? So, we published a letter and

simply said, “Pitts and McClure are right”. Taylor applied to NIMH for a grant, and the grant was awarded but at the same time the United States Navy called him to service and he left. I didn’t have anybody to take over the grant. One day, Don Klein asked if I would be offended if he took the Taylor protocol and completed it. My attitude was I couldn’t do it, so why not. By that time, I was interested in something else.

In my lifetime I’ve had a number of research fellows to whom I’ve suggested studies. One year, read about the dexamethasone suppression test (DST) by Bernard Carroll. I had a fellow from Greece working with me at Stony Brook, Yiannis Papakostos. I asked him to find out if it was true. I helped him design a protocol and get it through the appropriate hospital authorities. Eventually we were able to describe the dexamethasone suppression test in patients before and after ECT. Before treatment it is abnormal; afterwards it’s normal and when it’s abnormal again the patient has relapsed. So we felt Carroll was correct. That kind of experimentation is part of my history; there were a number of similar studies.

DH: Before we leave the drugs completely you also produced probably the first report about people having withdrawal problems from antidepressants.

MF: Yes. We were treating the patients at Hillside with imipramine, chlorpromazine, and other drugs, and, of course, we didn’t know what to do at the end of a trial. After six weeks treatment, we stopped the medication. There was no reason not to, whether the patient improved or not, since we did not have experience with long-term dosing. This was 1959 or 1960. I had a resident, John Kramer at the time, who told me about a patient who, he thought, had an upper respiratory problem but the internist found no infection. Her nose was running, she had back pain and had quit eating. Then another patient, and then a third had the same symptoms. I told Dr. Kramer to see every patient right after treatment stopped. He saw these "withdrawal" symptoms after chlorpromazine and imipramine and put together a paper with Don Klein on withdrawal symptoms to imipramine. It was published in the *American Journal of Psychiatry* in 1961. It was amazing, nobody had ever seen it or heard about it, but we did the definitive experiment, raising the dose to three hundred milligrams and then stopping; forty-eight hours to seventy-two hours later, patients had withdrawal phenomena which we described. It was a rewarding experience.

DH: When did you commence to use the EEG as a tool to look at what drugs were doing?
MF: I'm not sure of the first experiences, but at Bellevue Iused to order EEG's as a resident as a test for epilepsy. This was between 1948 and 1951. A treatment for epilepsy with phenytoin had been developed, I think in 1938. If you made a diagnosis of epilepsy on the EEG and behavior you could treat the patient. But more interesting was insulin coma. I'd already learned about EEG changes in frequency from alert to sleepy, to deep sleep, to stupor and coma. When I went to Hillside, it did not have an EEG. I applied for a Fellowship from the National Foundation for Infantile Paralysis and went to Mt. Sinai Hospital two days a week for a year to learn EEG with Hans Strauss who had published a textbook on EEG practice. I still worked at Hillside and after I was trained the hospital bought a Grass EEG instrument.

That purchase was a wonderful little story. The director Joseph S.A. Miller asked, "How much does it cost"? I replied, "Well, it's five thousand dollars". That was, a lot of money in those days. A few days later, I got a message to come to his office and he handed me a check for five thousand dollars, a grant from the Dazian Foundation. The hospital bought a Grass electroencephalograph, hired a young woman who I trained, and we started doing EEG's on everybody. We recorded the EEG during insulin coma. That's easy, but when I tried to do it during an ECT seizure I burned out parts of my instrument and had to have them replaced. I could record 24 hours later an inter-seizure EEG. That was the way I started to study the mechanism of ECT's action.

We set up a schedule of experiments so that an EEG was recorded a day after a treatment each week. We had records of patients who had 1 to 3, 4 to 6, 7 to 9, and 10 to 12 seizures. On the average, we gave twelve treatments. We didn't know why but nowadays, worldwide, depressed patients need six to seven treatments to achieve remission.

Using the same design we studied the effects of chlorpromazine and imipramine using 1200 mg of chlorpromazine and 300 mg of imipramine because these dosages were effective in 80% of the patients. We next studied the effect of amobarbital on the EEG. We showed that amobarbital changes the EEG effects of electroshock; if a patient has had three treatments and you give them amobarbital it looks like they've had six or nine treatments. We used to measure the EEG by hand with a ruler scoring the amplitude and

width of the waves. The width was expressed quantitatively as cycles per second. We examined six 10-second samples, to quantify 1-minute epochs. It became obvious in the first work we did that the EEG reflected brain function very, very dramatically; momentarily, and it was sensitive to changes in the patient. If a patient has an EEG running and I gave LSD, within three minutes we saw changes. You see the effects of amobarbital within a minute. Years later, when I did the first EEG measures of benzodiazepines, within a few cardiac cycles the EEG was showing induced fast waves. It's almost instantaneous; a most dramatic effect. This work formed the basis for two lines of subsequent research. sOne was my studies of EEG and electroconvulsive therapy and the second was my interest in quantifying the EEG. I became tired of hand measurements, and sought ways of doing it electronically. A report published in 1957 or 1956 described an electronic frequency analyzer developed in St. Louis by George Ulett, then Professor of Psychiatry at Washington University. I was impressed by his demonstration. George said he had all the material to build a frequency analyzer for me. I applied to NIMH for funding and it was awarded. He shipped the analyzer to Hillside Hospital and we were one of the first to apply a frequency analyzer for pharmaco-EEG studies in about 1958. That was also why I moved to St. Louis in 1962. George Ulett had been asked by the governor of Missouri, who had a crisis in his mental health system, to become Director of the Office of Mental Health. They had found that the nurses and aides were offering women patients for sex to outsiders, acting as pimps. After the governor fired the Mental Health director Ulett took over with the proviso that he could create an Institute for Research and he offered me an appointment as Director of the Institute. In 1962, I was also appointed research professor at Washington University and spent four years in St. Louis.

DH: Could you take me over the research you did after you moved to St. Louis?

MF: I'm going to go back a bit, because it was at the time I was working at Hillside that we began evaluating new drugs. Once the system had been set up for chlorpromazine and imipramine, every new psychotropic drug that came to Hillside was examined. In 1959, I was invited by Jonathan Cole to be part of the Clinical Drug Evaluation Committee of NIMH. That Committee set up what were called Early Clinical Drug Evaluation Units, ECDEU. We met a few times a year as investigators and as a grant-reviewing

organization. Dr. Cole had fifteen million dollars that we assigned to investigators around the country to study the new drugs. This was 1959 or 1960. One of the grant awards went to Hillside. The people on the committee were the people who'd done the work in the previous four or five years on drugs and each investigator were asked which aspect of psychopharmacology they were willing to study. Herman Denber, at Manhattan State Hospital, was a psychoanalyst as well as a psychopharmacologist and interested in the effects of drugs on the unconscious behavior of patients in groups. Some units were doing urine chemistry, so there were studies on the metabolites of chlorpromazine. I was interested in EEG and the first grant I had received was NIMH Grant M-927 for the study on the EEG effects of electroshock in 1954. The next grants were for pharmaco-EEG trials, although we didn't call it that. It was the effect of different drugs on the quantitative electroencephalogram.

In 1958 in Rome, at one of the early meetings of what became the CINP, my interest was matched by that of a group from Erlangen, Germany. I presented a report on the acute and chronic EEG effects of imipramine, chlorpromazine, and placebo. Imipramine and chlorpromazine showed EEG effects that differ from those of ECT. I was on a panel with presentations by Turan Itil who collaborated with Dieter Bente. Their paper was also on the EEG effects of chlorpromazine and imipramine. Their findings and mine matched. Afterwards, we got together and it was obvious that my slides and his were identical; it was amazing that in Germany and America we had the same findings. This technology separated the effects of two active psychotropic drugs. We hadn't finished the three drug study with Klein, but it was important that this was shown. We also knew at that time that other drugs had different EEG effects and for the next two or three decades the issue was "What can be learned from the EEG changes induced acutely and chronically"? That became the science of pharmaco-EEG.

In 1961, Itil wrote to me saying he would like to come and work with me in New York if I had the money. I said I did, but by the time he was ready to come, I had moved to St. Louis. Over the years he and his wife told me they hadn't known where St. Louis was. He came due to his interest and enthusiasm in pharmaco-EEG and because I had the equipment he lacked in Germany. In St. Louis, one of the first things I did was work with Washington University to develop a digital computer analysis of the EEG.

The first digital computer analysis of an EEG signal was presented in 1960 at UCLA at the opening of the Brain Research Institute. I was invited to attend and I brought back with me a strip with the quantitative energy scores of different frequency bands. I told Dr. Ulett that we should seek a digital computer analysis instead of the electronic frequency analysis. The work had been done at MIT and eventually we were one of the centers that started a digital computer analysis of EEG.

Our first digital computer was an IBM 1710, with key-punch and card reader for Hollerith cards. The memory was very small, but eventually we graduated to an IBM 1800, a much larger computer with more memory. From the first day that we conceived of this method of quantification the Federal government, the State of Missouri, and the State of New York gave me the money I asked for. It is phenomenal to realize that when I moved back to New York in 1966, I went to NIMH requesting $1.2 million dollars for this computer. I next received a letter saying if I was doing studies on psychotropic drugs could I also do some studies on drugs of abuse? Fortunately I was studying opiates so they gave me $1.2 million dollars for the equipment as well as annual support for personnel until 1975.

The importance of pharmaco-EEG was multiple. The first was that you could tell whether a drug was active or not on the brain, wheter it got through the blood-brain barrier. If it doesn't have an effect on the brain, it's not going to have an effect on behavior. That syllogism, that psychotropic drugs must first have an effect on the brain to have an effect on behavior, is still true and much ignored today. Sadly, no direct measurements of brain function are made to be sure that the drug has such an effect in humans.

Pharmacologists also argue that if an agent does have an effect on the cat, mouse or rat it must do the same in man. That syllogism is not true. We examined drugs that were active in the dog or in the mouse and rat that are not active in humans at the doses given, e.g., flutroline. The EEG differentiates the effects of the compounds; chlorpromazine from imipramine; imipramine from LSD and atropine from LSD. Atropine and imipramine are close, but we found differences. When the benzodiazepines became available they had a totally different profile. As Turan Itil has published, one can predict a drug's psychoactive effect from EEG studies in man. He worked out a quadrant

of four axes of EEG changes that are associated with the individual clinical effects of different drugs. When the EEG profile is on one pole, its clinical effects are of a particular class. Some drug profiles fall into several quadrants, offering different clinical effects in different doses and populations. If a drug is in both the antipsychotic and the antidepressant quadrants it's going to have effects on some patients as an antipsychotic and on others as an antidepressant.

We can also demonstrate whether a drug is pharmacologically active or acts as a placebo. We did multiple trials at different dosages and found some drugs which at one dose would have a suggestive profile but at a higher dose had a clear profile. And in some at an even higher dose we saw yet another profile. From these data we could predict the effective clinical dose range. Remember, all of our work is in humans. It's critically important to realize that the literature on EEG and drugs is split into ninety percent of work done in animals which is of little, if any, relevance to human psychopharmacology. Humans are a different species than rats, cats, dogs and definitely different from cats in their pharmacology. There was a wonderful symposium on EEG in animals and man at the Society of Biological Psychiatry about 1966. It is published as *Anticholinergic Drugs in Animals and Man*. edited by Philip Bradley and myself. In that book, there are articles on the effect of anticholinergic drugs in cats that differ from dogs, the monkey, and the mouse, all differing from the effects in humans. Man is different, so human pharmaco-EEG is a predictor of the clinical effects of psychoactive drugs.

DH: When all of this came out, how did the field respond, when you talk about humans but all these guys are working in rats, cats and dogs?

MF: When I began to present the EEG profiles of humans at the American EEG Society, there were a series of papers that appeared from America's leading pharmacologist at that time, Abraham Wikler, who was the expert on narcotics at the government Hospital in Lexington, Kentucky. He wrote a definitive text on pharmacology. Everybody used it and it went from hard cover to paperback. Wikler had done his work in dogs and at one meeting after another, would speak after me. He was much older than I and was very much respected. I was a young kid. He would say, "These findings are not at all what I see" and he would show his slides, and my data were ignored. It took awhile to realize that his work was in dogs, not humans. It's very important because the pharmacologists

believe with all their heart that animal trials are directly applicable to human studies. And a reason my work was disregarded was that I was much younger. Very few psychopharmacologists were doing human EEG work, other than Itil, Bente, Herrmann and a few others. We were a very small group. The Europeans, who were many more than the Americans, were not very assertive.

I visited Wikler's laboratory and saw his experiment where the dogs are suspended on belly slings. The electrodes are implanted going through cable to an electroencephalograph. Wikler administers an anticholinergic to the dog and the dog's legs are moving and the EEG is showing slow waves, but not showing the fast waves. Well, why didn't they show them? Because the movement of the legs are inducing artifact, so it is very rare to get a clean EEG. In my opinion, he's discarding the fast waves as artifacts. He's discarding essential data he interprets as artifact. The conflict seemed to resolve in 1968 when we published that book with Bradley. It became clear that pharmaco-EEG was a human discipline if you're going to be successful predicting drug effects in patients. Some in the pharmaceutical industry agreed, but then came the big issue of expense. Doing work in humans is not easy. Pfizer, to give them credit, had a relationship with a prison in Connecticut and asked would I be willing to set up an EEG laboratory so that their scientists could do pharmaco-EEG drug trials on prisoner volunteers. We set up the equipment, organized the recording protocols, and agreed to analyze the EEGs recorded on tape in New York. It was probably 1971 or 1972. Then Pfizer and all of the industry got a message that you can't do experiments in prisoners; paying them was unethical as they were not free agents; so the laboratory was closed.

The same difficulty occurred in Holland in another way. I was doing studies with the Dutch at Organon. Itil also studied a number of their drugs. For each drug, we did the analyses in volunteers and in patients. They realized they couldn't do patient research in Holland, so they asked if we would set up an animal laboratory. I argued that they would have to use animals close to humans, possibly chimpanzees. They set up a laboratory with, I believe, six chimpanzees. They educated a team, implanted electrodes, and trained the animals. They had a cable setup with a large computer. We gave them the computer programs. The physical facility was magnificent. First, they planned some pilot work with established agents, probably imipramine or chlorpromazine, to see if the

EEG's were like humans. Yes, they were. I was very excited. However, one day I got a message that four of the chimps had died and they were now down to two. Are two enough, they asked? I don't know, I replied. .Chimpanzees die when they're in a restrictive environment. I didn't realize this. Eventually the laboratory was closed. They continued with some rodent studies but these led nowhere.

Then, the new game in psychopharmacology became chemistry. Electrophysiology was pushed into the background and, suddenly, everybody was involved with neurotransmitters.

DH: But you had picked out some drugs using your approach, hadn't you?

MF: Two examples are important. One is a drug that Pfizer called flutroline, that the pharmacologists predicted would be "a one injection a week" drug, because a single dose blocked vomiting in dogs for a week. Human trials for safety were done and then clinical trials. First, I did an EEG study in human volunteers. I recorded the EEG profile at the dose they recommended, then at a higher dose, and then a dose which was far above what was accredited. None had an EEG effect. It just didn't do anything. We next tested six patients at the Northport VA with a history of psychosis not responding well to standard antipsychotics. After having the protocol approved and the patients' signed consent for a new drug treatment, we took them off their antipsychotic and replaced it with flutroline. In three weeks it was obvious that the drug, at the maximum dose I was allowed to give, had no antipsychotic effect. Experimentally, I increased the dose. It didn't do anything. Pfizer didn't accept it immediately. They set up additional clinical trials but, eventually, you have not heard of flutroline. We published the paper describing its potency in dogs and inactivity in humans in both EEG studies and clinical trials.

The other side of the coin was, of course, the experiment that was successful. On one visit to Organon they handed me documentation for testing the EEG profiles of six drugs. I could not handle six drugs in human trials at one time. I offered three files to Turan Itil who was in St. Louis with the same programs. His first was GB 94. I don't know how long later, but I received a call from Turan that he was sending me some GB 94 and would I do two subject trials. We did the paperwork, and then tested the samples in volunteers. I called Turan and I said, "This is very interesting; it's exactly like imipramine". He replied, "That's what I found. I'm going to tell them in Holland".

Turan phoned, and we were invited to Oss in Holland. Itil presented his work and I presented my two cases and they said, “This drug has the pharmacology of drugs that affect migraine and we’re supposed to evaluate it for migraine”. But they agreed to study it as an antidepressant and I organized an antidepressant trial in New York. They also sent it to Hungary and Czechoslovakia and in time all the clinicians agreed that it worked like an antidepressant. It is called Mianserin, and Organon marketed it, but not in the United States. It would not have been marketed as an antidepressant if it hadn’t been for the pharmaco-EEG studies.

DH: It actually did well in Europe.

MF: A best seller.

DH: Yes, for most of the 1980’s. As I understand it, the reason it failed in the US was that they picked the wrong framework for the trials.

MF: No, the failure of the trials was for a specific reason.

DH: The patients were too mildly ill; so they weren’t able to show a distinction between drug and placebo in the trials. Were there further issues?

MF: I’m going to tell you one of the issues.

DH: Please do. This is very interesting.

MF: Dr. Raoul Desjardins, a physician, was the head of a company that monitored commercial drug trials in the United States. He ran the trial, and we picked the sites together. After some months we visited the three sites and two months later we visited the three sites again and on the second or third visit, he became suspicious of the work records. I did not understand what his suspicion was, but as we left one of the trials in Boston, he said, “I’m going to come back with a team but I don’t need you.” Sometime later he called me and said, “I’d like you to come with me, we’re doing another site visit”. We went to the site and he asked the investigator, who’s well known, to please pull any chart. He pulls one and it’s incomplete; numbers are missing, dates are missing. Then, when I saw the master sheet has one date and the chart has another date I asked, “How did this come about”? The investigator replies, “Well, he’s taking care of it, ask him”, pointing to a clerk, a young man, probably a Bachelor candidate, not a physician or a nurse. Desjardins and I went to a second site and the records were also incomplete in the same way. Both sites had been selected for competence and experience. Everybody

agreed they were well known; both of them had NIMH grants. They were part of the pharmaceutical establishment. The one in Boston had too many drugs to study. In fact, some of the charts had two drugs recorded at the same time, which is unheard of, so that study was cancelled. The Dutch were faced with the dilemma of what to do with the data? They sealed the three studies in the submitted files to FDA but without request for FDA analysis or approval, and decided that they would pursue a sister drug, ORG-3770, mirtazapine. It had the same EEG profile. I'd published the paper to show that 6-asamianserin with two isomers had equivalent EEG patterns similar to that of mianserin. The pharmacologists in Holland thought that one isomer was active and the other was inactive. We did an EEG study in humans with isomer A, with isomer B, and the combination, with the same doses of isomer A and isomer B, and the combination at equivalent doses. The EEG response was the same for all three. It was published in *Psychopharmacology* in 1982. It's another fine study of the power of pharmaco-EEG trials. They made a business decision to wait and, a few years later, they came to America with it.

DH: With Remeron (mirtazapine)?

MF: Yes. It was after that, that all these newer agents were introduced with emphasis on this or that neurotransmitter. Mirtazapine was also more sedating than the public liked, which was true for mianserin, as well.

DH: True.

MF: Mianserin ended for various reasons, but I think sedation was one of them, was it not?

DH: There was a big fuss in Europe about it that it causing a drop in the white cell count.

MF: It's possible.

DH: This was around the period when drugs like fluoxetine (Prozac) came on the scene. I think the marketing of the SSRI's was much better.

MF: The director of research for Organon became a personal friend, his family and my family. He sent his daughter to America in 1976 to stay with us for a couple of months to learn English. His name was Jack Vossenaar. I asked: "Jack, with mianserin, did you get your money out of it"? "Max, I was promoted because mianserin worked". "Promoted"? "Yes, I became the overall director of research for the whole company; before I was only

in neuropharmacology, but they liked what I had done, so I became the director. You know, pharmaco-EEG worked".

DH: Absolutely.

MF: In the real world, what counts is money.

DH: Right, but we don't have it nowadays. How different would the field look, do you think, if we had more pharmaco- EEG now?

MF: My clinical experience with some of the new drugs is limited. I ended my clinical experience in 1997. From 1980 to 1997, I was a staff psychiatrist at University Hospital at Stony Brook, a thirty-bed unit, and during the six months that I was on rotation I cared for the patients in fifteen beds and taught the residents. The other six months I would teach and do research. When the new drugs came in, like fluoxetine, we were not doing pharmaco-EEG studies anymore. That ended at Stony Brook in 1986, mainly because finances dried up; industry wouldn't support it; NIMH wouldn't support it; although, Jonathan Cole was anxious to continue it. More importantly, my interest had shifted to ECT.

DH: What was your experience with fluoxetine?

MF: My first experience with fluoxetine was with inpatients. We gave it to patients at increasing doses. It didn't work very well. When it seemed to fail we gave the patient imipramine or ECT and the patient improved. Again the drug had limited success.

DH: What about atypical neuroleptics?

MF: At the doses that had been recommended, I saw no effect on cognition, no sedative effect and no effect on any of the physiologic measures that I experienced with other drugs. I would say today that if the pharmaco-EEG analysis of the atypical neuroleptics and the new antidepressants were to be done, they would show little difference from placebo at the doses that are recommended. Whether they might be of some benefit at higher doses is unclear. Some EEG studies of these drugs are reported but the studies are poorly done, not well controlled. The pharmaco-EEG world ended about 1990. We had developed a fine technology and methodology for dosing, quantification of the EEG that created a science. But some clinicians did not use quantitative measures; they would look at the wiggles and say, it works or it doesn't work.

The classic story is that of clozapine (Clozaril). In the 1990s, a poster session came out on EEG with clozapine at different doses. It came from NIMH, and said at high doses the drug produced seizure activity; they recommended the limit should be set at a dose before seizure activity, monitored by blood levels. After that the efficacy of clozapine declined. Nobody benefited at the lower doses. In order for clozapine to be effective the EEG has to show the changes that an untutored EEG observer might call "abnormality". Well, what's an abnormality? An EEG with seizure-activity is a normal effect of clozapine at effective doses. The benefit comes from the seizure-like activity. I don't know what the physiology of these high voltage slow waves with spikes is, but it is not "abnormal". It is normal with clozapine. I believe that every patient successfully treated with clozapine will exhibit spikes and slow waves; it is normal for that drug.

DH: I want to quickly take you to the history of the field. The conventional histories of all the people that have been interviewed here for the last ten or fifteen years would say that the field began with chlorpromazine in 1952. They would say that chlorpromazine is the best effective agent we have to treat people who've got mental illness. I know you don't think that's the case; that it began twenty years earlier with the use of barbiturates to treat catatonia. Could you take me through the history of that, and also how you came into the area?

MF: The catatonia story?

DH: Yes.

MF: What a delightful question! When I was a resident at Bellevue, I went on the wards in psychiatry in a little white coat. It had two side pockets and pens in a breast pocket. In one pocket, I had a box containing a syringe and needles. Every night these were sterilized by autoclave. In order for the needles to be sharp, I sharpened them myself. That's the level we were at. In my other pocket, I had two wooden tubes containing amobarbital sodium (Amytal) 500 mg each and a tourniquet. Very often, a nurse or an aide would call me to an excited patient in restraints, or one who was a posturing catatonic, or a manic. The catatonic patient was easy; put a tourniquet on and inject amobarbital. The most dramatic thing occurred; patients who were posturing, mute and not feeding would quickly respond and talk or begin eating. A few hours later they would be back in their posturing, back in their mute state. I didn't realize it at the time

but those patients were all sent for ECT. I did not work at ECT in my residency at Bellevue. So, I just didn't see it.

DH: How was the effect of amobarbital on catatonia recognized?

MF: The story is documented in a magnificent silent film from 1930 that is available at the National Library of Medicine. William Bleckwenn described the effect of amobarbital on four catatonic patients, each posturing with arms outstretched. One patient was rigid with the legs up and head up, in a U shape position. After amobarbital he is seen talking. You see his mouth moving but the response is not heard. Bleckwenn has a line on the bottom: "The patient is catatonic" and then the box says, "2 grams amobarbital." The next person is walking back and forth after being pictured posturing and still. Another is a woman, sitting frozen and staring, and next you see her eating, she's hungry and she's moving both hands to feed herself. That was the beginning of psychopharmacology in the modern era.

Four years later, Ladislas Meduna in Hungary treated his patients by inducing seizures. Psychiatrists in Hungary found Meduna's the original records of Meduna's experiments experiments at the hospital called Lipótmetsö. A paper on that is gong to appear this March (2009) in the *Journal of ECT*. Of Meduna's first eleven patients, nine were catatonic: five were mute and tube fed.; four were posturing and rigid. I can only say that God was good, if there is a God, because had Meduna first selected schizophrenic patients of the paranoid or hebephrenic types he would not have obtained the positive results that he did with the few seizures that he induced. Catatonia is immediately responsive to ECT. In my work at Hillside, St. Louis and New York I paid little attention to catatonia. Like many others, when the drugs came, I assumed that catatonia had disappeared. I didn't see it very often; my students, however, did. Richard Abrams and Michael Taylor wrote three fine papers on catatonia in manic patients in 1976 and 1977.

My interest in catatonia began in 1987 at Stony Brook. I was in charge of ECT, and one day Gregory Fricchione, a Harvard graduate, the attending in charge of the Consultation-liaison service, said he had a patient on the medical service that was catatonic and he thought I should give the patient ECT. The patient had been in the hospital for many weeks, was being tube fed, had an IV, and was in restraints

periodically. She had malignant catatonia with both the manifestations of excited and stuporous catatonia. I used to give “hands-on” courses in ECT and that day I had four students. We did the consultation together. One student is now a professor of psychiatry at a medical school. The others are practitioners. We agreed that she was catatonic with a history of mania. The patient had lupus erythematosus and the lupus expressed itself in a catatonic state. I asked: “Would any of you be willing to give this patient ECT”? Three students said, no, because she’s too sick. But, the future professor of psychiatry said, “Max, you’re not going to treat this woman, you can’t, she’s going to die” and he was the most emphatic. The other three were not sure of themselves. I wrote my chart note saying: “Accept for ECT immediately, but if we’re going to give the patient ECT, we will give treatments three days in a row” and I signed my name. The medical department, the parents and husband all went into panic. A week went by. Greg Fricchione asked whether I would meet with the family. I did, and pointed to the reality that she was dying; she was losing weight and the internists had given up on her. Consent was given and we treated the patient. She recovered dramatically. She left the hospital, fully capable of walking and talking. Then I told Greg to send me any catatonic he found and I would treat them.

Over the next few months he referred other catatonic patients, then another patient in manic delirium. On the day of the second ECT, the manic calmed down and no longer needed restraints. The day of the third ECT, he said, “I want to go home”. It was most dramatic. That got me interested in catatonia. The lupus case was published in 1990 in the *American Journal of Medicine* and after that I got in touch with Mickey Taylor. In 1991, Taylor and I published our first paper on catatonia; how to identify it and argued that it should be separated from schizophrenia in the upcoming revision of the classification. In the next decade we worked together and in 2003 we published *Catatonia: A Clinician's Guide to Diagnosis and Treatment*, in which we covered everything that we could find in the literature and from our experience. We have since argued to make catatonia as a specific entity in DSM5, in “a home of its own”. In 1980, a commentary in *Psychological Medicine* asked “Where Have All the Catatonics Gone”? I don’t know where they’ve gone since we still find them in about 10% of in-patient psychiatric services; they’re just not often recognized. Actually nowadays, catatonia is

being recognized as a motor syndrome. We urge the use of lorazepam (Ativan) as a specific diagnostic test. If the patient responds to an intravenous dose we recommend treatment with lorazepam at high doses. Eighty percent of the patients meeting our catatonia rating scale criteria at Stony Brook responded to lorazepam. Twenty percent had to be treated with ECT, a pretty good record, I think. Incidentally, every person that we'd treated, except three, at the time we wrote the book had recovered. Three patients did not recover and each failure we view as the result of inadequate treatment.

DH: In the wider public mind, the thing you're most interested in is ECT. Now, you've been part of ACNP from the start. ACNP hasn't always been the friendliest organization for ECT. Can you link those two stories together for me?

MF: When ACNP started, about a third of the members were clinicians; physicians treating psychiatric patients and carrying out drug studies. About a third of the members were psychologists, most often interested in behavior measures; and a third were laboratory chemists and physiologists. In the first decade there was a strong emphasis on the clinical issues including an interest in EEG. We held a number of pharmaco-EEG panels. There was also some interest in ECT. At the time, we discussed the conditions for which ECT was applicable, as in patients who don't do well with antidepressants or antipsychotics. In the early 1970s the California legislature restricted the use of ECT, and the treatment became "controversial". Members of the ACNP, by and large, cut off interest in ECT. Since 1980, there's been zero interest. There's been some nascent recent interest because of the enthusiasm for brain stimulation as a new gimmick. A Brain Stimulation Symposium is scheduled for this afternoon. There was one either a year or two ago.

My active involvement with the ACNP was at the very beginning. I was a member of a number of the committees. I was chairman of a Nominating Committee the year that we nominated Nathan Kline, which, by itself, caused a furor, because Nathan Kline already had a reputation as being somebody who did multiple trials, etc. Nevertheless, he was a leading clinical figure and became President. Originally, there was some interest in the ACNP in such things as, "How Does One Make A Diagnosis"? I had two evening sessions on "catatonia" that worked out very well, because there were people in the audience who stood up and said, "You're imagining things, you're seeing

cases we never see; they don't exist." More recently interest in these topics has been non-existent, not only here, but also in the New Clinical Drug Evaluation Units (NCDEU) and Biological Psychiatry meetings.

A few years ago I was appointed to the ACNP History Committee and I chaired it for a year and had a wonderful time. The function of the History Committee at that time was only to invite an annual lecturer. We had debates on who to invite. Now, they've taken over the Archives and that's an interesting feature. My own archives are at the University of Stony Brook Library, rather than here.

DH: Most people from the outside see in ACNP a group interested in the physical treatments given people who are depressed or have schizophrenia. But you're at odds with that in the sense that you've seen the drug treatments push ECT out of the field. Could I ask you to talk about that?

MF: ECT began in the 1930s, and at first in America and around the world, it was very actively used. For two reasons; one, most of the patients who were mentally ill were in big mental hospitals and ECT was a way of reducing the mayhem that occurred in the hospital. A wonderful paper described the reduction in the number of fires set and the number of windows broken after ECT. Then chlorpromazine came, in in the 1950s and imipramine, in the 1960's. Studies were done in which patients were randomly assigned either to ECT or imipramine, or ECT or one of the other antidepressants, or ECT or chlorpromazine. There was even one study of ECT vs. monoamine oxidase inhibitors (MAOI). When these were published in the early 1960s, they all said essentially the same thing. The criterion for evaluation was dischargeability; the rating scales and the dischargeability criteria showed that the drugs were equivalent to ECT. Not really equivalent when you look at the data, particularly in some specific studies published from California in which the ECT was superior, but the difference was not that big. Instead of having a 40% remission rate with drugs, ECT developed 48% to 52% remission rates. The end result was to discard ECT for two reasons: one was that ECT was not done well,.doctors weren't interested and there was no science behind ECT. The second was that if they were almost equivalent ECT could be put aside since pills are easier to use, less expensive in manpower, and more easily accepted by the public and patients. Also, the doctor did not have to leave his office. Some studies reported better results for ECT in

depression, mania, and schizophrenia but this was a mixed bag. Some of those diagnosed as “schizophrenics” were major depressives with psychosis; some, in retrospect, were surely catatonic and responded very well; and ome were obviously chronic hebephrenic and paranoid, and did not respond well. So, a dichotomy of ECT response was reported. It was also that some who responded responded within the first six to eight treatments wheras for others it took twenty-five or more. The attitude developed that ECT was difficult to use and not much better than pills.

The appearance of Scientologists was another factor. Then some liberal minded academics like Thomas Szasz and Peter Breggin, as well as former patients, began to attack ECT. Physicians faced with the choice of maintaining ECT as a practice and dealing with Scientology or, as in California, with restrictive laws, opted out and no longer considered ECT for their patients. California passed a law in 1973 that restricted the use of ECT. Doctors went to court and the court agreed that the California legislature could not restrict ECT, restrict practicing medicine. The California legislature then passed a new law requiring detailed recording of treatments, including ECT and lobotomy and that created a big limitation. They also passed, as part of that law that anybody under eighteen had to have an adult other than the parent give permission. So about 1975 ECT essentially stopped in California. The American Psychiatric Association created a Task Force, which met from 1975 to 1978, and their report in 1978 said ECT is very effective for certain conditions and defined them. It also said ECT is a treatment that needs more research on methodology and that we were unclear about equipment and monitoring seizures. Most importantly, the report said that ECT required voluntary written consent. That was the first time the American Psychiatric Association argued that the patient must give his or her signed written consent for a psychiatric treatment and the consent issue has become fundamental in clinical ECT. To this day, a written consent for a psychiatric treatment other than ECT is not required in most states. Basically, a physician can prescribe any medication and forcibly give any medication if the patient is a risk to himself or to others. We can’t do that with ECT. And, so, by the late 1970’s and early 1980’s, ECT effectively disappeared from America and around the world.

DH: You are now seen as the key person in insuring that ECT did not disappear completely. How did you get pulled back into these issues?

MF: It's a very interesting story. When I left Hillside Hospital in July 1962, I moved to St. Louis as Director of the Missouri Institute of Psychiatry. We had patients, the chronically ill, kind of patients usually seen in state hospitals. I did not open an ECT unit in the four years I was there. We did everything with psychotropic drugs. ECT in many hospitals and many research units disappeared. When I came back to New York I did not open an ECT unit until 1968, and the way that happened was partly research and partly happenstance. New York Medical College did not have an ECT suite or unit. A resident named Richard Abrams came to me. He had spent two years in the United States Army Medical Corps and wanted to do a study of unilateral vs. bilateral ECT. I went to the local Gracie Square Hospital where ECT was an active service and said I would like to do a research project and could fund it. They agreed. I wrote a grant application to NIMH and asked for funds to compare unilateral vs. bilateral ECT as well as multiple treatments in one session (MMECT) vs. single treatments in a series. I equipped an EEG laboratory, put an air conditioner in the wall, and hired a nurse from the New York Medical College who would come to the hospital, when we needed her. Most interesting was the NIMH site visit. We were asking for three years support and they requested a timeline of what I expected to do each six months. When I got to the end of the fifth six months I still hadn't finished the data collection. One of the site visitors, Arnold Friedhoff of NYU, said he thought I needed four years support and so the grant was awarded for that. That study showed that bilateral ECT was better than unilateral ECT and that multiple monitored ECT had more risks compared to single treatments and it was not more effective. Those papers were published in, I guess from 1971 to 1973. The work was done between 1968 and 1972. I was appointed to the APA Task Force on ECT because I published those papers. The studies were well controlled, well monitored, using EEG monitoring and rating scales.

DH: At this point you had done the research but you hadn't become firmly committed to the idea that ECT had to be saved, had you?

MF: In 1978, I was an author of the *APA ECT Task Force Report*, and after the report was published a number of hospitals, encouraged by the positive nature of the report, decided to start an ECT service, and invited members of the task force to give a lecture or help set up a service. I had a manual on how to do that. At that point I also became

interested in the mechanism of ECT and in 1979 I took a sabbatical from Stony Brook to write a book on ECT. There's an odd personal issue there. The Task Force had five full members and two advisory members, so there were seven votes on any recommendation. On a number of issues, the words in the manual were written after a vote of four to three. I said if we weren't sure of the answer we should leave it open, inviting research clarification. But the Task Force wanted to give guidance to the field. So, those four to three votes gave me heartache. At the end, I was almost ready not to sign the document. Then, I decided to write my own book and, in 1979, I wrote *Convulsive Therapy, Theory and Practice* that was published by Raven Press in New York. I took every issue that had been arbitrarily decided by the Task Force and explained the pluses and minuses of what was known. That book is, I think, the best I've written on ECT, even compared to the new one. So that was how I got interested in reviving ECT.

Another push came when NIMH organized a meeting of ECT researchers in 1978. There had been an earlier meeting in 1972 the proceeding of which was published as the *Psychobiology of Convulsive Therapy*. The meeting was organized by NIMH and held in Puerto Rico. It took awhile to get the papers published by V.H. Winston and Sons, in Washington DC, in 1974. That book described the neurophysiology, biochemistry and neuropsychology theories at the time. Those were the three elements discussed with not a word about endocrinology.

By 1977, the APA ECT Task Force had presented some of its conclusions, and the NIMH agreed to the second investigators' meeting in New Orleans in May of 1978. At that meeting the issues were different. Mechanism was the focus, and one session was devoted to "Could Endocrines be an Issue." Jan-Otto Ottosson presented his ideas and a very similar experience occurred to what had happened with Itil and me in 1958. Independently, we had read the literature and had come to the conclusion that the peptides in the hypothalamus must be a factor in the recovery process after ECT. The evidence we used were the DST and TSH response data with some other neuroendocrine material. We published our neuroendocrine theory in 1980. Next, I applied for and got money to do further research on ECT. We were interested in how to monitor effective seizures and the outcome of treatment. Many of the studies at that time lacked EEG monitoring, so when the doctor said the patient had eight treatments and yet did not get

well, we did not know whether the seizures had been adequate. We were able to argue that you have to record, a seizure duration of at least 25 seconds or longer and show EEG seizure activity of slow waves and spikes, and to have a sharp end point as markers of an effective treatment. It took a while to develop those criteria. Looking back, many of the studies of the 1980s and 1990s were done poorly. To this day, there are reports published in which a depressed patient has failed drugs and ECT but when I look at what this meant, in many instances it was not the ECT that failed, but it was the the clinician who had failed by failing to develop adequate seizures. It was the same as prescribing pills without ensuring the patient takes them.

DH: A lot of people would say you're the person who did most to save ECT in the US and maybe, worldwide. Is that the thing you wish to be remembered for, or is it the catatonia or the pharmaco-EEG story? Or should all of these that you should be remembered for?

MF: That's a wonderful question. I have recently taken my archives, which are all my records from 1950 to a year ago, and deposited them at the University Library at Stony Brook. As part of that process I opened some of the boxes. At first I was going to censor the material and then, I thought, this is nonsense. It's not for me to decide. The world will decide twenty years or thirty years from now whether pharmaco-EEG was an error in science or an important step in learning. They surely will learn about ECT. They might learn about my work with opioids and opioid antagonists. The issue about my life is that I was a researcher, who learned early the importance of control studies, random assignment, monitoring, and independent evaluations. I learned all the things which make up a wonderful study; that's what I tried to do. If you ask what the best papers are, is that reasonable?

DH: It is.

MF: My paper on chlorpromazine and insulin coma I consider very important. It had a profound effect on my career, because the hospital then gave me a lot of money and whatever I asked they were glad to give it to me. Then, NIMH gave me money and I expanded my research quickly. By 1958 we closed the insulin coma unit. Other important studies were monitoring the ECT and the 1972 conference on theory. In 1958 I had written a theory of ECT based on neurophysiology. It's called *The Neurophysiologic*

Adaptive Hypothesis. I applied to NIMH many years later to test the theory. Richard Abrams, Jan Volavka, Rhea Dornbush and some others worked on the project; that was done at Gracie Square Hospital. We concluded that the neurophysiology measures were an index of immediate response but were not related to therapeutic outcome, that the neurophysiologic theory was wrong. In retrospect, the study failed to support the theory because we didn't have proper diagnoses for the patients. If we had tested the theory in relation to catatonia or melancholia it would have worked, but in those days patients referred for ECT had a variety of diagnoses. We confirmed that ECT requires seizures and that the mechanism is not in the neurophysiology changes we measured but was inherent in the seizure.

The second ECT mechanism I hypothesized was the "cholinergic hypothesis". That was published in 1966, and was not supported. The third hypothesis was published in 1980 with Ottosson and that's the "neuroendocrine hypothesis". I would like to think that the "neuroendocrine hypothesis" at the present time is still the best explanation of ECT.

I did some of the first experiments with naloxone in opioid dependence, at the same time as the people in Lexington and, following our work, it became obvious that everybody should have Narcan freely available in emergency units, so that they could give naloxone to patients admitted to the hospital in stupor or coma. The first time this happened I received a call from a hospital in New York City. I was at home in Great Neck, Long Island and drove into the city; they had a man in stupor secondary to opiate overdose. I gave him naloxone IV and he woke up. It was a very dramatic experience, the fact that naloxone actually wakes up an opioid dependent subject. But then I made a fundamental error; naloxone was short acting and I did not take that into account. Opioids are long acting and the patient went into stupor again after I had left. I got another call. I told the resident ito get another batch of naloxone and to inject it again, as often as necessary. In the morning we had given him naloxone every 2 to 3 hours until the opioids were gone, the best demonstration of naloxone's efficacy.

With pharmaco-EEG we developed a quantitative science, showing that the quantitative EEG was a worthwhile measure of drug effect using digital computer methodology. I'm sad there was commercialization of the pharmaco-EEG model. I heard

that in California some doctors are promoting pharmaco-EEG as a predictor of drug effect in the individual and of clinical diagnosis. That's nonsense; it does not work. What the pharmaco-EEG record can tell you is whether a drug is active or not; it does not give a diagnosis.

Then, I got interested in catatonia and suddenly realized that catatonia is not schizophrenia. Working with Mickey Taylor, we published a book about that and I'm working very hard to convince the DSM5 Task Force to put catatonia in a category by itself; "in a home of its own."

After Taylor and I finished our catatonia study and our book was published, we met in Chicago. We discussed our finding that catatonia is remarkably responsive to benzodiazepines and to ECT. We had only three treatment failures, but many, many successes. When you take the catatonia rating scale and give lorazepam to a patient; if the symptoms resolve, even temporarily, by a fifty percent reduction in the scale that is, a verification of the diagnosis of catatonia. The validation is when you give the patient high doses of lorazepam or ECT. In our study at Stony Brook, we had thirty plus patients that followed this protocol. Everybody labeled as "catatonia" was given a lorazepam test. The 82% who had a positive response to the single dose of lorazepam had a positive response to lorazepam treatment at high doses. But 18% did not respond to lorazepam. We gave them ECT and they all resolved. So, catatonia is a definable entity. It is a biological syndrome. It should be a separate entity in the DSM and I hope I'm alive to see it.

If the commissioners don't include it as a separate entity, then it's a repetition of the earlier errors in DSM-I to IV, which is purely descriptive and not based on biological etiology.

My next contribution is in melancholia. After publishing *Catatonia,* Taylor and I were celebrating at brunch in Chicago and asked what are we going to do next? Taylor said, "There is one other condition that responds to ECT and that's melancholia". But what is melancholia, and how do you define it? We worked for three years and wrote *Melancholia: A Clinician's Guide to Diagnosis, Pathophysiology and Treatment of Depressive Disorders*, which was published in 2006 by Cambridge University Press. We argue that "melancholia is a syndrome", a mood and motor syndrome, which is defined

by specific characteristics. They are depressed people with vegetative and motor signs; they have symptoms in all three areas. When these patients are examined for cortisol function, a large percentage, we don't have a definite number have elevated serum cortisol and failure to respond to the steroids that suppress cortisol. When a melancholia patient with all three characteristics plus cortisol abnormality, is treated with a tricyclic antidepressant (TCA) in adequate dosage there is an 80% response rate. That's what the old literature shows. We don't have a new drug study to prove it, but with ECT there is a 90% resolution of melancholia within three weeks. And if the cortisol abnormality does not resolve, that's a sign the patient needs more treatment. So, cortisol abnormality is an index of severity of illness and of the presence of this type of depression.

DH: All the people interviewed say that the ACNP helped them hugely. In your case, in terms of ECT and melancholia, catatonia and pharmaco-EEG, how has the ACNP helped, or have you been at odds with the organization?

MF: In the first decade, Itil and I and others submitted symposia, clinically related, about pharmaco-EEG and they were accepted on the program. We ran two or three hour sessions before there were posters. We also offered ECT sessions and they were accepted. So, every other year we would have an ECT session or a pharmaco-EEG session. I said that badly; Pharmaco-EEG was active before ECT. ECT came in the 1980's, and we had a number of symposia at that time, not well attended, but they were here. Once we learned the mechanism of ECT with the neuroendocrine hypothesis we had one symposium in the late 1980's, and that was it. Then, whenever we submitted symposia, they were rejected. A symposium was suggested for this meeting. Dr. Lisanby of Columbia University was the senior author and it was rejected again. I have always considered the ACNP as not very supportive of anything that I did regardless whether it was insulin, ECT, pharmaco-EEG, or psychiatric diagnosis. I've been outside the mainstream of the society, especially when it became enamored with laboratory neuroscience. Rather than a College of psychopharmacology, once they turned to neuroscience, clinical issues disappeared. About ten or twelve years ago, Donald Klein got very upset with this society. He and I submitted clinically related symposia but they were rejected. Klein then organized the American Society of Clinical Pharmacology, ASCP. I was an original member and that society still exists. For a while, it had funding

from private sources, but now they are also dependent on industry funding. They do not have a meeting with individually submitted presentations. They run annual teaching sessions that give attendees a test after the sessions and award certificates of attendance in psychopharmacology. They invited me once or twice to teach a session, but they, too, are not interested in ECT, in the EEG or in clinical syndromes other than bipolar disorder and anticonvulsants, depression and SSRIs, and schizophrenia and atypical antipsychotics; subjects of interest to the pharmaceutical industry. If you were to ask Don Klein at this point, I think he would say that the ACNP has become too neuroscience-oriented, that the clinicians; physicians, psychologists and sociologists have all disappeared and the symposia now are mainly related to industry projects and proposals, or to fantasy neuroscience.

DH: A big concern at this meeting has been the issue of links to industry, how people who've been senior figures in the field have ended up on the front pages of *The New York Times*. How do these issues look to you, the links between ACNP and industry, and where do you think the future lies?

MF: I knew of the control by industry in the late 1980's when they took over the American Psychiatric Association. Parallel to my experience with ACNP, I submitted symposia to the APA and they usually turned me down. They would accept a symposium on ECT or NMS every once in awhile. It would be presented Thursday afternoons, the last session, the last afternoon, and I'm sensitive to that. The APA had a task force in on ECT in 1978 and another that met and produced a book in 1990. We had a symposium the next year and the year after, but following that they turned down our submitted symposia and I got upset. I believe that the APA has been fully taken over by industry. They say they're trying to change that, but I have my doubts because the APA is so beholden to industry to support their exhibits and the thousands of people that they bring from overseas. The ACNP has made an attempt, I understand, to deal with this issue but the leaders of the society are intimately tied to industry.

This morning I walked into a paper session here. A member of this society Michael Thase put up a slide showing his association with industry for conflict of interest and the audience roared, there was big laughter. He offered the list of his consultancies and research grants, there must be forty, maybe fifty on the list. And what did he say

when showing the list; “Because I work for every company, nobody influences me!”, and the audience roared again. That defense is silly. Leaders of this organization are intimately tied to industry and they do not provide data that would permit a reasonable clinician to evaluate the benefits and risks of the new drugs, in order to prescribe optimally. I have said, publicly, that I have stopped using any drug produced after 1980. None have been tested independently and with time their inefficacy and risks are better understood. I will not recommend any drug unless it was tested before 1980. That’s not altogether true. There are some new drugs in medicine that are fantastic, like etanercept (Embrel) for psoriasis, but in psychopharmacology I know of no new drug that has been effectively tested and for which we know the positive and negative aspects with confidence. The data are very strongly compromised and I am sorry that this society has not taken a stronger position. They say they’re doing it and I hope so but the fact that three former presidents have gained notoriety in the newspapers, and a few others probably will, makes me very nervous. I also am concerned that the DSM-III and DSM-IV have been very poor models for diagnosis and treatment and I am trying very hard to get DSM-V to consider catatonia and melancholia as separate entities. For catatonia we can make the diagnosis based on behavior, verify it by laboratory tests, validate by treatment with an outcome of ninety percent or better. The same is true for melancholia. That’s what I think should be done. But as I’ve talked to people today and I met with skepticism. I am tilting at windmills and I suppose that’s a good way to end this interview. I’ve been a Don Quixote figure for a long time.

DH: Okay.

MF: Thank you very much.